Pediatric Focused Safety Review: Singulair (montelukast sodium)

Pediatric Advisory Committee Meeting

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Outline

- Background Information
- Pediatric Studies
- Pediatric Labeling Changes
- Additional Relevant Safety Labeling
- Brief History of Neuropsychiatric Events with Montelukast Use
- Drug Use Trends
- Adverse Events
- Summary

Background Drug Information
Singulair (montelukast sodium)

- **Therapeutic Category:** leukotriene receptor antagonist
- **Sponsor:** Merck & Co., Inc.
- **Indication**:
  - Prophylaxis and chronic treatment of asthma in patients 12 months of age and older.
  - Acute prevention of exercise-induced bronchoconstriction (EIB) in patients 6 years of age and older.
  - Relief of symptoms of allergic rhinitis (AR):
    - seasonal allergic rhinitis (SAR) in patients 2 years of age and older
    - perennial allergic rhinitis (PAR) in patients 6 months of age and older.

Background Drug Information
Singulair (montelukast sodium)

- **Dosage (by age)**
  - 15 years and older: one 10-mg tablet.
  - 6 to 14 years: one 5-mg chewable tablet.
  - 2 to 5 years: one 4-mg chewable tablet or one packet of 4-mg oral granules.
  - 6 to 23 months: one packet of 4-mg oral granules.
- **Administration (by indications):**
  - Asthma: Once daily in the evening for patients 12 months and older.
  - **Acute prevention of EIB: One tablet at least 2 hours before exercise for patients 6 years of age and older.**
  - SAR: Once daily for patients 2 years and older.
  - PAR: Once daily for patients 6 months and older.

Background Drug Information
Singulair (montelukast sodium)

- **Original Market approval:** February 20, 1998
- **Pediatric labeling changes:** March 26, 2012
  - Exercise-induced bronchoconstriction (EIB) indication expanded down to include patients 6 to 14 years of age.
  - PREA studies waived for ages 0 to 5 years.

Pediatric Studies: Safety and Efficacy for EIB
Singulair (montelukast sodium)

- Multinational, randomized, double-blind, placebo-controlled crossover study with the 5 mg chewable tablet in patients age 6 to 14 years (n=64)
  - Singulair given as a single dose followed by exercise challenge testing at 2 hours and 24 hours.
  - Primary endpoint: mean maximum percent fall in FEV1 at 2 hours post-dose exercise challenge.
    - Statistically significant reduction in EIB compared to placebo.
  - Similar results at the 24-hour time point support the durability of the effect.
  - However, review of the pediatric responder data showed that some patients were not protected from EIB at 24 hours post-dose.

Pediatric Labeling Changes Singulair (montelukast sodium)

8.4 Use in Specific Populations, Pediatric Use

- Safety and efficacy of SINGULAIR have been established in adequate and well-controlled studies in pediatric patients with asthma 6 to 14 years of age. Safety and efficacy profiles in this age group are similar to those seen in adults *[see Adverse Reactions (6.1), Clinical Pharmacology, Special Populations (12.3), and Clinical Studies (14.1, 14.2)].*
- The safety and effectiveness in pediatric patients below the age of 12 months with asthma, 6 months with perennial allergic rhinitis, and 6 years with exercise-induced bronchoconstriction have not been established.

Pediatric information included throughout labeling for EIB for patients 6 years and older.

Relevant Safety Labeling
Singulair (montelukast sodium)

4 CONTRAINDICATIONS- Hypersensitivity to any component of this product

5 WARNINGS AND PRECAUTIONS

5.1 Acute Asthma

5.2 Concomitant Corticosteroid Use

5.3 Aspirin Sensitivity

5.4 Neuropsychiatric Events

5.5 Eosinophilic Conditions

5.6 Phenylketonuria

Relevant Safety Labeling
Singulair (montelukast sodium)

5.4 Neuropsychiatric Events

- Post-marketing reports include: agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor.
- The clinical details of some post-marketing reports involving Singulair appear consistent with a drug-induced effect.
- Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with Singulair if such events occur [see Adverse Reactions (6.2)].

Relevant Safety Labeling
Singulair (montelukast sodium)

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

- The most common adverse reactions (incidence ≥5% and greater than placebo; listed in descending order of frequency) in controlled clinical trials were: upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, otitis.
- The safety profile of SINGULAIR, when administered as a single dose for prevention of EIB in pediatric patients 6 years of age and older, was consistent with the profile above.

Relevant Safety Labeling
Singulair (montelukast sodium)

6 ADVERSE REACTIONS

6.2 Postmarketing Experience

- Psychiatric disorders: [see Warnings and Precautions (5.4)].
- Nervous system disorders: drowsiness, paresthesia/hypoesthesia, seizures.
- Sponsor has made the following change to section 6.2 in labeling: “Renal and urinary disorders: enuresis in children.”

Brief History of Neuropsychiatric Events with Montelukast Use

- FDA began reviewing FAERS data and clinical trial data for association with leukotriene receptor antagonists in 2008
- Early Drug Safety Communication released by the FDA in March 2008
  - Announced the review of possible association between montelukast and behavior/mood changes and suicidality
  - Reporting of events to FAERS increased
- Resulted in addition of Neuropsychiatric events to Precautions section of montelukast label in August 2009 (now Warnings and Precautions in PLR format)

Neuropsychiatric Events in FAERS (n=400) February 20, 1998 to March 26, 2008

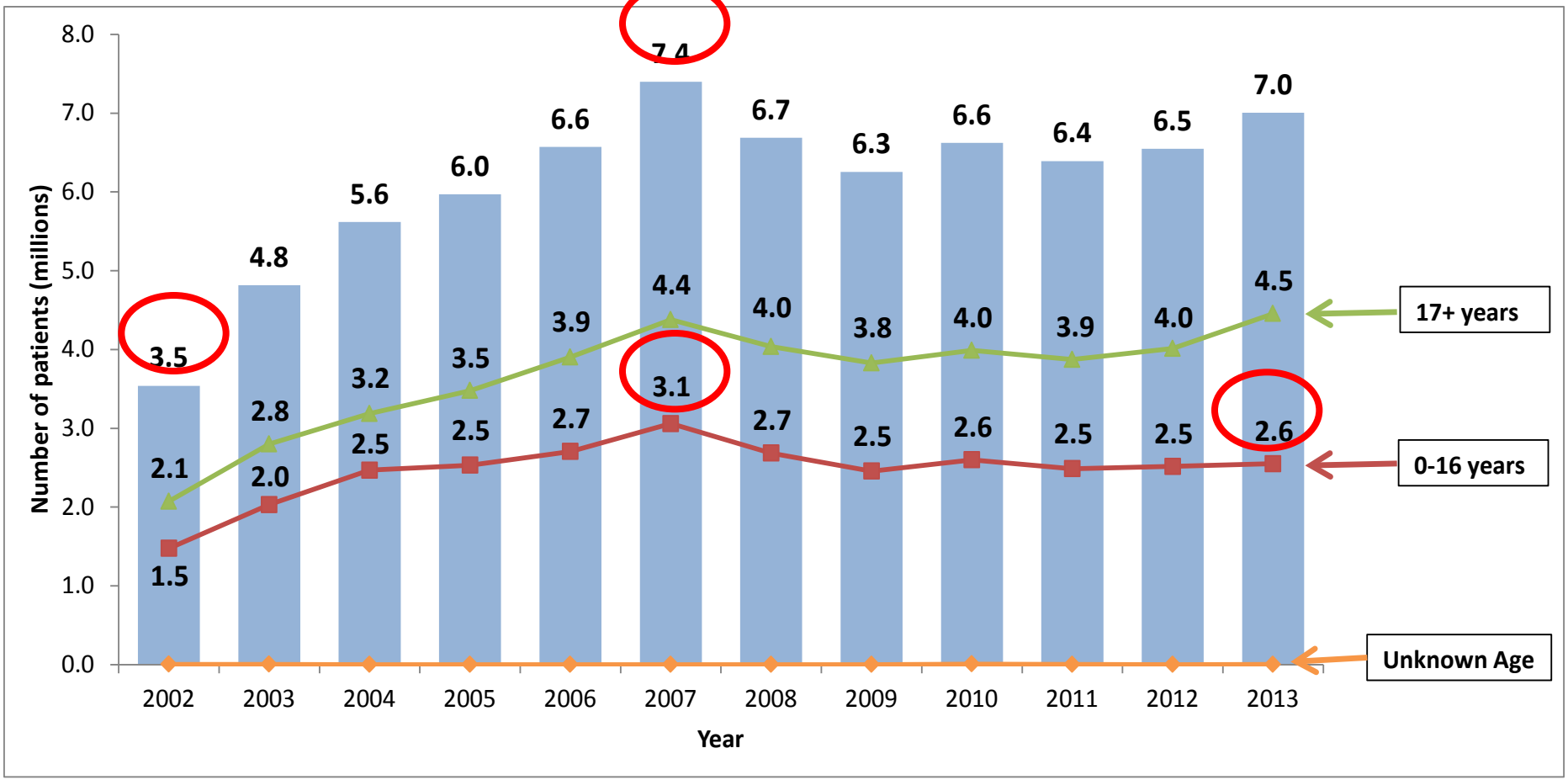
- Half of cases reported in pediatric patients <17 years (50%)
- Most common reason for use: Asthma (64%)
- Broad set of neuropsychiatric events reported Sleep disorders and Disruptive behavior most commonly reported
- Compelling cases in FAERS
  - Positive rechallenge reported in 34/400 cases
  - Positive dechallenge reported in 226/400 cases
- Cases appeared to be consistent with drug-induced effect

Pediatric Focused Safety Review

Singulair Use Review

Since Pediatric Labeling Date
(March 2012 through September 2013)

Patients receiving dispensed prescriptions for montelukast by patient age from U.S. outpatient retail pharmacies



Source: IMS Health, Vector One®: Total Patient Tracker. Years 2002-2013. Data extracted August 2014.

Patients receiving dispensed prescriptions for montelukast by patient age

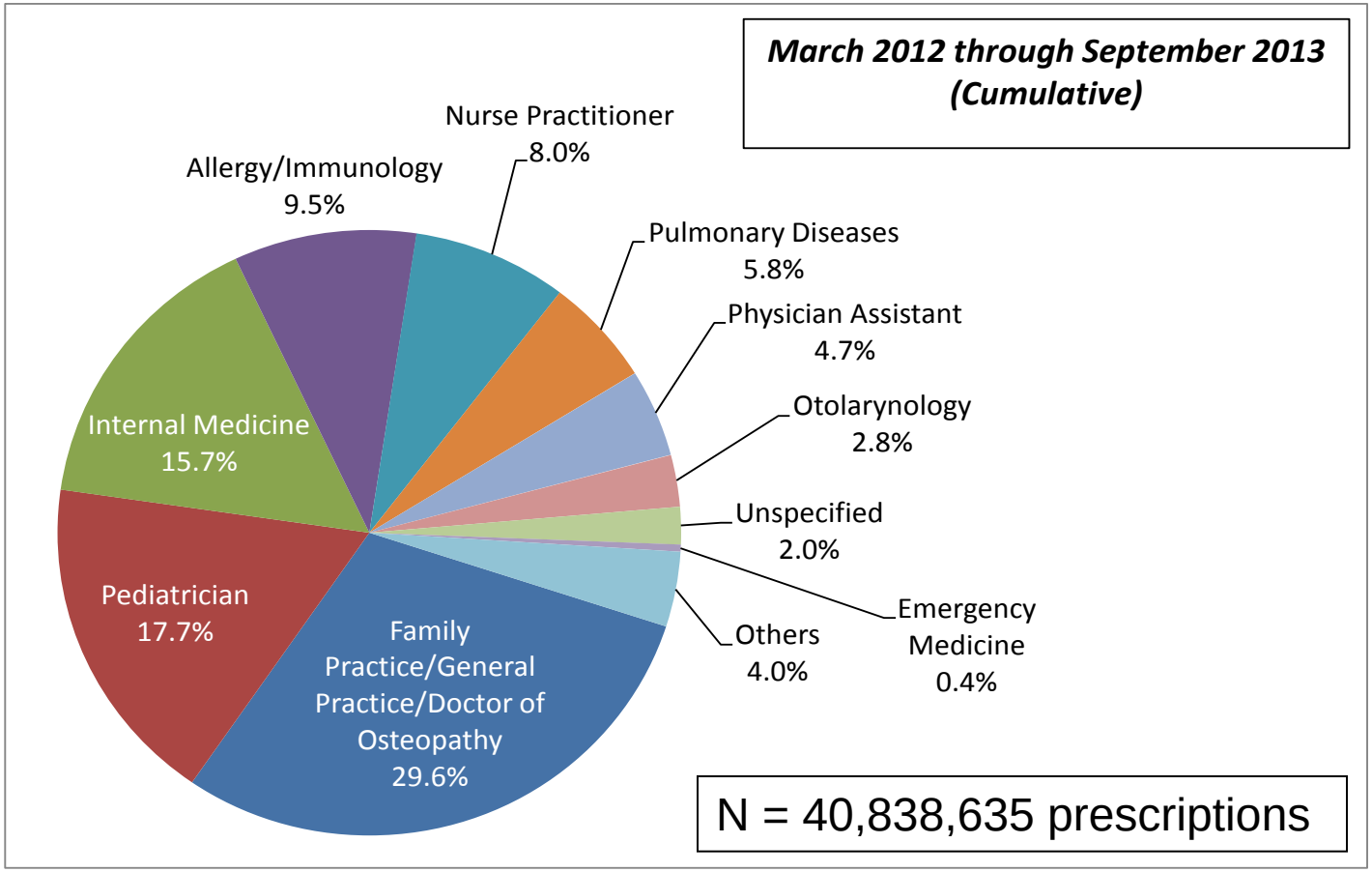
	Cumulative 3/2012-9/2013	
	# of Patients	% Share
Total Patients	**8,798,502**	***100.00%***
0-16 years	3,307,328	*37.59%*
0-1 years	200,588	*6.06%*
2-5 years	955,779	*28.90%*
6-11 years	1,562,665	*47.25%*
12-16 years	872,092	*26.37%*
17+ years	5,500,621	*62.52%*
Unknown Age	2,232	*0.03%*

Source: IMS Health, Vector One®: Total Patient Tracker. March 2012 to September 2013. Data extracted May 2014.

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

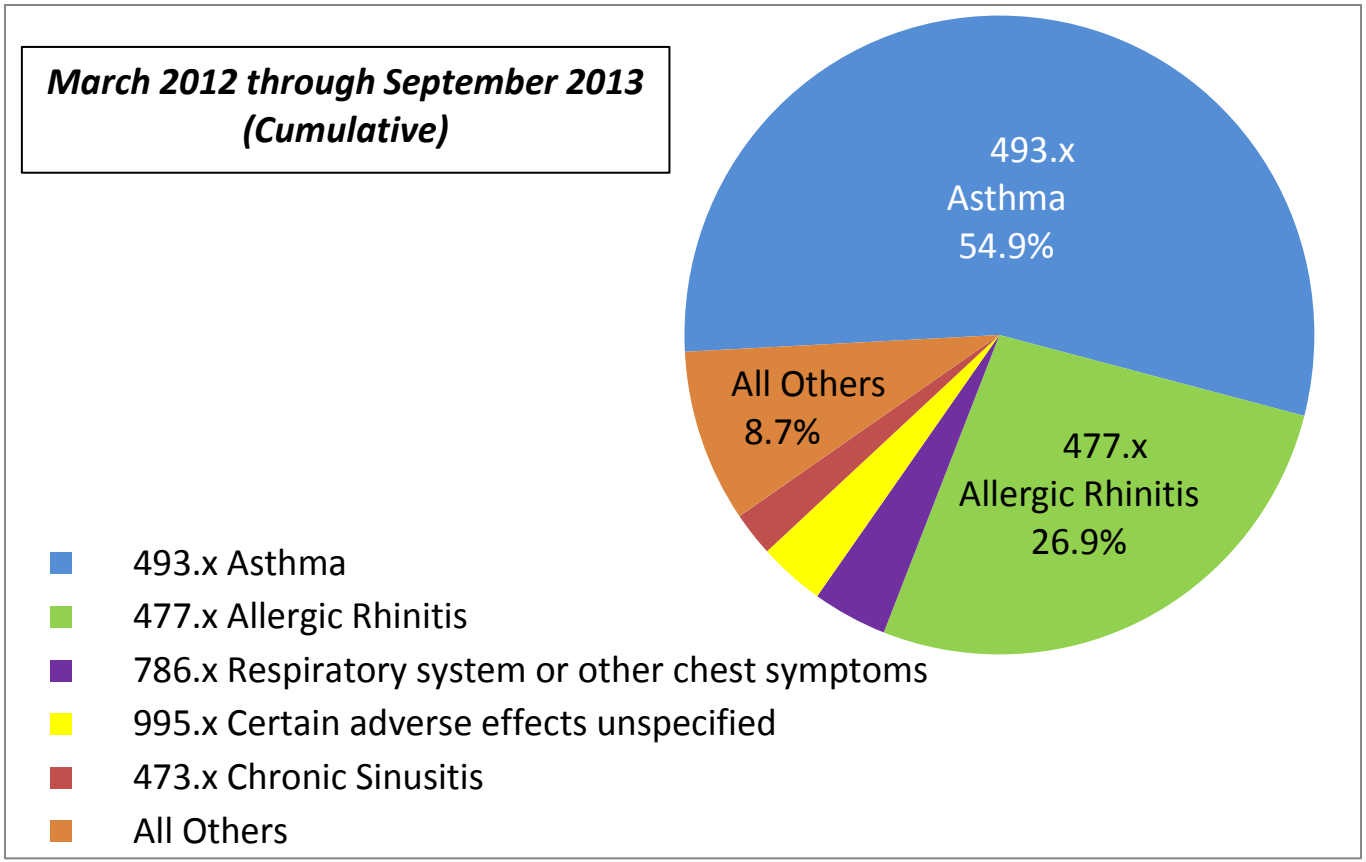
**Summing patients across patient age bands is not advisable and will result in double counting and overestimates of patient counts.

Top 10 specialties prescribing dispensed prescriptions for montelukast from U.S. outpatient retail pharmacies



Source: IMS Health, National Prescription Audit™. March 2012 to September 2013. Data extracted May 2014.

Top 5 diagnoses associated with montelukast use in *pediatric patients (0-16 years)* as reported from U.S. office-based physician practices



Source: Encuity Research, LLC., TreatmentAnswers™. March 2012 to September 2013. Data extracted July 2014.

Total Number* of Singulair Adverse Event Reports Since Pediatric Labeling Change (March 26, 2012- September 26, 2013)

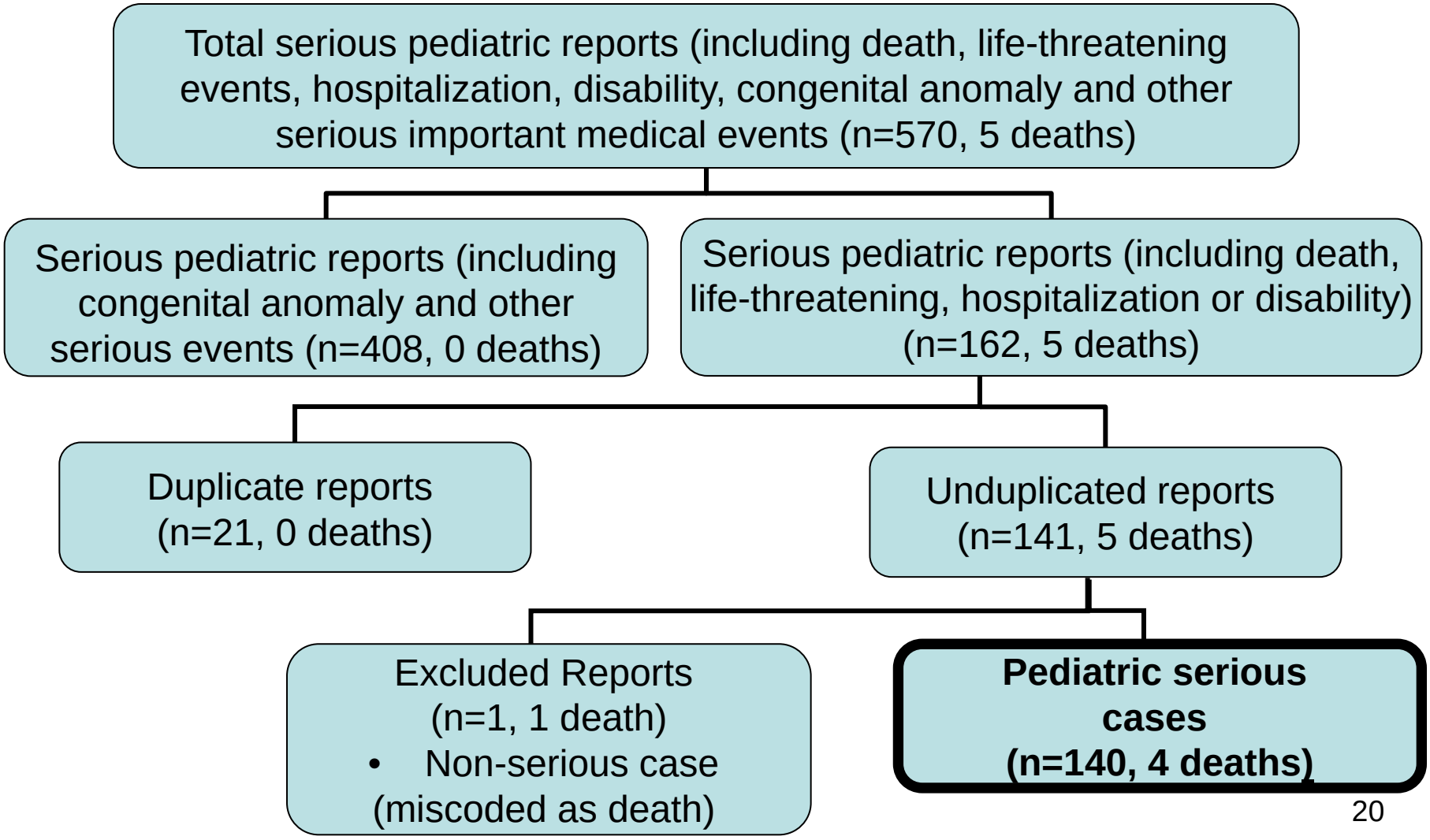
	All reports	Serious**	Death
Adults (≥ 17 yrs.)	1148 (905)	915 (674)	75 (60)
Pediatrics (0-<17 yrs.)	731 (579)	570 (422)	5† (5)

*May include duplicates and transplacental exposures, and have not been assessed for causality

**Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

†No additional cases of pediatric deaths were identified among cases not reporting an age.

Case Selection of Serious Pediatric Cases



Demographics of Serious Adverse Events Singulair (montelukast sodium) (n=140)

- Age (n=140)
  - 12-<17 years (n=40)
  - 6-<12 years (n=57)
  - 2-<6 years (n=36)
  - 1 month-<2 years (n=7)
- Gender
  - Male (n=77)
  - Female (n=62)
  - Unknown (n=1)

Serious Adverse Events
Singulair (montelukast sodium) (n=140)

- Deaths (n=3 labeled, 1 unknown cause)
- Psychiatric disorders (n=64 labeled, 11 unlabeled)
- Nervous System disorders (n=16 labeled, 5 unlabeled)
- General disorders and administration site conditions (n=7 unlabeled)
- Hepatobiliary disorders (n=4 labeled)
- Immune System disorders (n=3 labeled, 2 unlabeled)
- Respiratory, thoracic and mediastinal disorders (n=4 labeled, 5 unlabeled)

Serious Adverse Events
Singulair (montelukast sodium) (n=140)

- Gastrointestinal disorders (n=1 labeled, 2 unlabeled)
- Skin and subcutaneous tissue disorders (n=1 unlabeled)
- Miscellaneous events (n=2 unlabeled)
- Vascular disorders (n=3 unlabeled)
- Blood and lymphatic system disorders (n=1 labeled, 2 unlabeled)
- Cardiac disorders (n=2 unlabeled)
- Endocrine disorder (n=1 unlabeled)

Singulair (montelukast sodium) Fatal Adverse Events (n=4)

- 2-year-old male received montelukast for asthma and experienced aggression, crying, ear pain, gait disturbance, insomnia, and pyrexia recurrently following administration with subsequent death from unknown cause. No psychiatric history provided.
- 16-year-old male taking montelukast as needed for allergies and asthma for 3 years and committed suicide one day after discontinuation of montelukast for unknown reason. Concomitant medications: fluticasone/salmeterol and albuterol (as needed during strenuous exercise). No psychiatric history provided.

*Unlabeled events are underlined.

Singulair (montelukast sodium) Fatal Adverse Events (n=4) (continued)

- 12-year-old female with no history of depression started Singulair for asthma and allergic rhinitis. After 3-4 years, she switched to generic montelukast and became irritable and moody with insomnia, but compliance was low. She was also taking fluticasone/salmeterol, which was discontinued. She restarted brand Singulair and long acting beta agonist with improvement in mood. Singulair was discontinued, but behavioral changes persisted and she committed suicide 4 months after initial behavioral symptoms were noted. No family history provided.

- 9-year-old male with no history of depression/mood disorders died from "an apparently self-inflicted gunshot wound". He had been taking montelukast 5mg for approximately 7 ½ years and no additional medications. No further information was provided.

Comment: Except for gait disturbance, remaining neuropsychiatric adverse events are labeled; one case where cause of death unknown.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Psychiatric (n=11)

- Obsessive-Compulsive disorder (n=4)/Psychotic disorder (n=2)
  - 3 cases reported a positive dechallenge.
- Tourette's disorder (n=2)/Tic (n=1)/Excessive eye blinking (n=1)
  - 5 and 9-year-old males developed Tourette's disorder after taking montelukast for an unknown period of time. Outcome was unknown in both cases.
  - 2-year-old male developed various motor tics 4-5 months after taking montelukast. Discontinued at age 8 years and tics decreased in intensity and frequency.
  - 7-year-old male on montelukast for treatment of multiple allergies developed excessive eye blinking. Positive rechallenge. Outcome unknown.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Psychiatric (n=11) (continued)

- Abnormal behavior (n=1)
  - 3-year-old female taking montelukast for allergies experienced "questionable emotional behavior" consisting of laying down and crying "for no apparent reason", and wanting to be a "baby" again that resolved within 4 days of discontinuing the medication.

Comment: Insufficient data to determine causality.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Nervous System Disorders (n=5)

- Abasia (n=1)
  - 4-year-old male started montelukast for asthma and seasonal allergies. He developed knee pain at 11 years of age which became so disabling that was unable to walk by 15 years of age and was treated with Vicodin, Flexeril and plasmapheresis; therapy continued without recovery of symptoms. No further information provided.

  Singulair Labeling- ADVERSE REACTIONS: arthralgia, myalgia

- *Loss of consciousness (n=1)*
  - *12-year-old female experienced loss of consciousness, bradycardia and pallor 5-10 minutes after starting montelukast, which recurred and resulted in cardiac resuscitation. Outcome unknown*

- Vestibular disorder (n=1)
  - 15-year-old female experienced nausea and vertigo on montelukast 10 mg (total daily dose, duration and indication unknown). Hospitalized and diagnosed with neurovegetative dystonia with marked psychosomatic signs and peripheral vestibular syndrome.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Nervous System Disorders (n=5) (continued)

- Intracranial pressure increased (n=1)
  - 8-year-old male developed elevated intracranial pressure and eosinophil count; and visual disturbance after starting montelukast. Other suspect† therapies: loratadine, homeopathic medications (unspecified), beclomethasone dipropionate, and albuterol

  Singulair Labeling- CLINICAL PHARMACOLOGY- eosinophilia

- Speech disorder (n=1)
  - 7-year-old male started montelukast for asthma after unknown duration developed speech disorder, gait disturbance, medication error, and somnolence. Other suspect therapy: quetiapine Concomitant medications: fluticasone and salmeterol. Outcome unknown.

  Singulair Labeling- OVERDOSAGE: somnolence

Comment: Single cases with limited information to determine causality.

†Suspect therapies- drug(s) suspected of causing the reaction as determined by the reporter.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

General/Administration Site Conditions (n=7)

- Product substitution issue (n=4)
  - Worsening asthma/bronchiolitis after switched from brand to generic.
- Unspecified adverse event (n=1)
  - 2-month-old female placed on montelukast for unspecified chronic pulmonary disorder and hospitalized for 2 weeks for an unspecified problem. Outcome unknown.
- Drug ineffective (n=1)
  - 15-year-old male with asthma started on montelukast and hospitalized because "drug ineffective and asthma". Multiple other suspect respiratory medications.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

General/Administration Site Conditions (n=7) (continued)

- Reaction to drug excipient (n=1)
  - 13-year-old female with food allergies experienced lip swelling 30 minutes after cetirizine ingestion. Generic cetirizine contains lactose. Other suspect medications: fexofenadine and montelukast.

  Note: montelukast also contains lactose.

Comment: many cases confounded by concomitant medications or insufficient data to assess causality.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Immune System Disorders (n=2)

- Dermatitis exfoliative (n=1)
  - 9-year-old male started montelukast for atopic dermatitis and contact dermatitis and after unknown duration experienced exfoliative dermatitis and disease recurrence requiring hospitalization. Concomitant medications: tacrolimus, mometasone furoate, cetirizine hydrochloride, fluticasone propionate/salmeterol xinafoate, and doxepin hydrochloride. Outcome unknown.
- Systemic lupus erythematosus (SLE) (n=1)
  - 14-year-old male started montelukast for unknown indication and after unknown duration developed SLE. Other suspect therapies: desloratadine, clomipramine, and budesonide/formoterol fumarate. Treatment information and outcome unknown.

Comment: Cases confounded by co-suspect medications.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Respiratory/Thoracic/Mediastinal disorders (n=5)

- Respiratory failure (n=2)
  - 5-year-old female with egg/cow protein allergy on montelukast presented with respiratory failure, jaundice, muscle weakness, vomiting and drowsiness 4 hours after receiving varicella vaccine. Recovered after hospitalization.
  - 9-year-old female started montelukast for asthma hospitalized with respiratory failure, asthma, asthmatic crisis and cyanosis. Other suspect therapies: fluticasone and salmeterol. Treatment information and outcome unknown
- Obstructive airways disorder (n=1)
  - 13-year-old male with history of allergic rhinitis and epilepsy admitted to ICU for respiratory failure due to asthma attack, requiring mechanical ventilation. Nasal budesonide, short-acting bronchodilators, formoterol, montelukast, and prednisolone initiated, but disease progressed and he was started on omalizumab. Montelukast held and asthma was controlled. Primary suspect drug reported as budesonide.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Respiratory/Thoracic/Mediastinal disorders (n=5) (continued)

- Apnea (n=1)
  - 7-month-old female being monitored at the hospital for upper respiratory infection received a 4 mg sachet of montelukast oral granules for asthma. She aspirated the granules and subsequently developed apnea.
- Pulmonary tuberculosis (TB) (n=1)
  - 9-month-old male with family outbreak of TB after starting montelukast for recurrent obstructive bronchitis also developed TB. Also taking budesonide. Three other siblings affected with TB who were not taking montelukast. Recovered following anti-TB therapy.

Comment: Many of these events can be attributed to the underlying disease state; TB case associated with family outbreak of TB; and in one respiratory failure case patient received varicella vaccine.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Gastrointestinal disorders (n=2)

- Celiac disease (n=1)
  - 5-year-old female with asthma and anemia started on montelukast and after unknown duration developed celiac disease and diarrhea. Other suspect therapies: esomeprazole magnesium and iron supplement. Concomitant medications: prednisolone sodium phosphate and an infant formula (Neocate powder). Treatment information and outcome unknown. No family history provided.
- Colitis (n=1)
  - 24-month-old female treated with montelukast experienced chills, clostridium difficile colitis, rectal prolapse, decreased appetite, diarrhea, fatigue, fungal infection and headache. One or more of the events was considered to be disabling and required intervention to prevent permanent damage/impairment. No further information was available.

Comment: Celiac disease case confounded by concomitant medications; colitis case lacked sufficient data to assess causality.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Skin and Subcutaneous Tissue Disorders (n=1)

- Hair loss (n=1)
  - 12-week-old male started on montelukast 4 mg daily for RSV infection and experienced hair loss at the temporal and parietal areas, erythroderma in the diaper area with touch sensitivity and positive Nikolsky's sign†. The patient was hospitalized and montelukast was discontinued. Concomitant therapies included fluticasone, cholecalciferol, and sodium fluoride. Outcome unknown.

Comment: Single case without relevant clinical information (such as time to onset or outcome of the event) to determine the relationship between hair loss and montelukast.

†- skin finding in which the top layers of the skin slip away from the lower layers when slightly rubbed.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Miscellaneous Events (n=2)

- Visual impairment (n=1)
  - 11-year-old male started on montelukast for asthma and 7 months later experienced visual disturbance and headache and was hospitalized. Therapy with montelukast sodium continued and the visual disturbance and headache persisted. Concomitant therapy: budesonide. No further information is available.
- Fall (n=1)
  - 4-year-old female with unspecified rhinitis started on montelukast for asthma. 2 months later, experienced headache, language disorder and fall without trauma, and was hospitalized. Cerebral CT scan was normal. Montelukast was discontinued. The patient recovered from the events. Concomitant therapy: albuterol, budesonide, loratadine, and mometasone furoate.

Comment: Events confounded by concomitant medications; limited clinical information to assess causality.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Vascular Disorders (n=3)

- Post-procedural hemorrhage (n=1)
  - 2-year-old female with multiple upper respiratory infections and "bronchial episodes" since 8 months of age, adeno-tonsillar hypertrophy and bilateral serous otitis underwent "adenoidectomy with transtympanic drainage"
  - Complicated by right cervical/adenoid inflammation and treated with prolonged courses of multiple antibiotics, varying inhaled steroids (including budesonide) and albuterol.
  - Immune deficiency suspected and she was started on Singulair 4 mg daily.
  - Due to symptoms of tonsillar hypertrophy with high obstructive syndrome, she underwent "tonsillectomy and adenoidectomy"
  - Complicated by two episodes of postsurgical bleeding of the bilateral amygdala, both requiring return to the operating room.
  - Maternal history of hemorrhage and fraternal history of abnormal activated clotting time reported. Lab evaluation for hematologic disorder incomplete.
  - Other concomitant therapies: acetaminophen, codeine, and amoxicillin.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Vascular Disorders (n=3) (continued)

- Hematoma (n=1)
  - 6-year-old female started on montelukast and after unknown duration experienced hematoma and decreased platelet adhesiveness requiring hospitalization. Suspect therapies: esomeprazole, albuterol, fluticasone/salmeterol. Treatment information and outcome unknown.
- Henoch-Schonlein Purpura (HSP) (n=1)
  - 45-month-old male with gastric reflux placed on montelukast for asthma and developed intermittent symptoms of HSP including abdominal pain, and diffuse joint swelling. Treated with prednisone and hospitalized. Montelukast discontinued 2 months after initiation. Outcome unknown.

Related Singulair Labeling- WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS and PATIENT COUNSELING sections: vasculitis consistent with Churg-Strauss syndrome.

Comment: Events confounded by concomitant medications and potential underlying disease; limited clinical information to assess causality.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Blood and lymphatic system disorders (n=2)

- Burkitt's lymphoma stage II (n=1)
  - 10-year-old male enrolled in atopic dermatitis study and started pimecrolimus 1% cream. 5 months later, diagnosed with Stage II Group B Ileocecal Burkitt's Lymphoma. Azathioprine, tacrolimus, and montelukast were co-suspect medications. Following severe immune complications, including a liver transplant, patient was in remission.
- Leukemia (n=1)
  - 5-year-old male started montelukast for asthma and was diagnosed with leukemia 2 years later. He discontinued montelukast and 2 months later experienced exercise induced bronchospasm and weakness. He was started on chemotherapy with improvement of leukemia.

Comment: Events confounded by concomitant medications; limited clinical information to assess causality.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Cardiac disorders (n=2)

- Tachycardia (n=2)
  - 10-year-old female started on montelukast for asthma. 4 months later, experienced tachycardia, chest pain, vomiting with hospitalization. Montelukast, desloratadine and fluticasone/salmeterol discontinued with recovery. Suspect therapies: desloratadine and fluticasone propionate/salmeterol.
  - 8-year-old female started montelukast for unknown respiratory disorder. After known duration experienced tachycardia, headache, flushing, muscular weakness, and paresthesia requiring hospitalization. Other suspect therapies: desloratadine, terbutaline sulfate, salmeterol, and omalizumab. Concomitant medications: albuterol. Treatment information and outcome unknown.

Comment: Events confounded by concomitant medications; limited clinical information to assess causality.

*Unlabeled events are underlined.

Serious Non-Fatal Unlabeled Adverse Events Singulair (montelukast sodium)

Endocrine disorder (n=1)

- Type I Diabetes Mellitus (n=1)
  - 8-year-old female started on montelukast for unknown indication. Approximately 1 month later, developed Type I Diabetes Mellitus requiring hospitalization. Other suspect therapies: cetirizine. Outcome unknown.

  Zyrtec (cetirizine) labeling: ADVERSE REACTIONS: diabetes mellitus

Comment: Single event confounded by other suspect medications.

*Unlabeled events are underlined.

Summary Pediatric Focused Safety Review Singulair (montelukast sodium)

- This concludes the pediatric focused safety review.
- As a result of PREA requirements, Singulair is approved for Exercise-Induced Bronchoconstriction in patients 6 years and older.
- Many events had single cases, confounding factors or limited information from which to draw causality.
- The safety review identified no new signals.
- FDA recommends continuing ongoing surveillance.
- Does the Committee concur?

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